

Body Mass Index, Follicle-Stimulating Hormone and Their Predictive Value in In Vitro Fertilization

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Purpose: The objective was to explore whether body mass and day 3 follicle-stimulating hormone have predictive value on odds of pregnancy after in vitro fertilisation. Few studies show that obesity produces a variety of alterations in the reproductive system, and that women with an elevation of day 3 FSH have declining ovarian function.

Methods: The data of one-hundred-seventy-one women who underwent a standard regime of controlled ovarian hyperstimulation was analyzed with particular reference to variations in body mass and hormone levels.

Results: By raising BMI and FSH (mIU/mL) by one unit, the odds for pregnancy were decreased by the respective factors 0.84 (95% confidence interval 0.73–0.97) and 0.77 (95% confidence interval 0.59–1.00).

Conclusions: The results demonstrate that for the purpose of raising the odds of pregnancy BMI should be reduced. A low FSH value may cause the same effect. Nonetheless, *obesity and hormonal function may be independent risk factors* for failure in assisted reproduction.

KEY WORDS: BMI, body weight, FSH, IVF, pregnancy outcome.

INTRODUCTION

Obesity is often seen as potentially treatable threat to the success of assisted reproduction, and while patients are commonly advised to try to normalize their weight before undertaking in vitro fertilization (IVF), many find weight loss difficult (1). Couples with infertility often wonder whether lifestyle habits might compromise their *ability to reproduce. Weight is one lifestyle factor that can affect fertility* (2).

Many indicators have been proposed to help in predicting controlled ovarian hyperstimulation (COH). Levels of serum follicle-stimulating hormone (FSH),

oestradiol (E₂) and luteinizing hormone (LH) on cycle-day 3 have proved to be sensitive indicators of ovarian response (3). It has been demonstrated that women with an elevation of day 3 FSH have declining ovarian function (4) and decreased success at treatment with assisted reproductive techniques (5–7). In addition, advanced female age and extremes of body mass are believed to have an adverse effect on the outcome of assisted reproduction (8).

Obesity as defined by a body mass index (BMI) of more than 30 kg/m² produces a variety of alterations in the reproductive system (9). In natural cycles, the fertility of obese women is lower compared to women with normal weight, and ovulation disorders are more frequent (10). Abdominal obesity, in particular, impairs fecundity and reduces the conception rate during infertility treatment (11–13). For anovulatory infertility in obese women, weight loss is a recognized treatment (13–16). However, the effect of body weight on the outcome of IVF has been

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controversially discussed. Some studies showed less IVF success in obese women while others did not demonstrate a negative effect (1,17,18).

We, therefore, conducted a study based on our collected clinical database, where *the odds of pregnancy after COH associated with IVF were analyzed* with particular reference to variations in the body weight and hormone levels of our patients in order to ascertain the extent to which body mass and hormonal function affect IVF outcome.

MATERIALS AND METHODS

Population

The data of one-hundred-seventy-one women who were referred to the Reproductive Medicine Unit at the Vienna University Hospital for IVF between January 2001 and December 2002 were collected for this retrospective study.

All selected patients had regular cycles and were undergoing a standard regime of controlled ovarian hyperstimulation. Patients with the following attributes were excluded: presence of severe endometriosis, a single ovary which might have precluded a normal ovarian response and any ovarian cyst measuring >10 mm in diameter *on a baseline day 2 scan*. Only women with a currently known height and weight having their initial cycle of treatment were included.

Before the couples were enrolled into our IVF programme, they underwent a standard protocol of investigations including a blood sample assayed for serum basal FSH, LH, E₂, TSH and prolactin (PRL) concentrations, which was taken on days 1–3 of the cycle prior to the onset of treatment. Basal serum FSH (mIU/mL) was measured utilizing an electrochemoluminescence immunoassay (ECLIA; Elesys 2010, Roche Company, France). Intracytoplasmic sperm injection (ICSI), as described by Van Steirteghem *et al.*, was performed for couples with severe semen abnormalities where <100,000/mL motile spermatozoa were recovered after sperm preparation (19). In cases of obstructive azoospermia, surgically retrieved spermatozoa from epididymis or testis were used for ICSI.

Stimulation Protocol

Patients received stimulation with recombinant FSH (rFSH) or human menopausal gonadotropin (hMG) after long-term gonadotropin releasing hormone agonist (GnRHa) down regulation (88 patients) or with a combination of cetrorelix acetate and rFSH

(83 patients). During GnRHa/rFSH or GnRHa/hMG treatment, 0.5 mg/day of buserelin (Suprefact®, Aventis Pharma, Bridgewater, New Jersey, USA) was given from day 21 of the previous cycle. Pituitary desensitization was considered complete after 14 days if serum E₂ was <50 pg/mL. Subsequently, follicular development was stimulated with rFSH (Gonal F®, Serono, Switzerland) or hMG (Menopur®, Ferring Pharmaceuticals, Denmark) at an initial dose of 150–300 IU/day (11).

The other stimulation treatment comprised administration of 0.25 mg cetrorelix acetate (Cetrotide®, Serono, Switzerland), starting on day 6 of ovarian stimulation with recombinant gonadotropins (150–300 IU/day), and was continued throughout the gonadotropin treatment period.

With each regimen, 10,000 IU human chorionic gonadotropin (hCG; Pregnyl®, Organon, Holland) was injected via the i.m. route when three or more >18 mm follicles were seen on ultrasound scan. The aspiration of follicles (transvaginally under ultrasonic guidance) was timed for 36 h later. Oocytes were fertilized by IVF or ICSI. One to three embryos were transferred 72 h after oocyte collection, using a Wallace catheter (Edwards–Wallace Catheter, Portex Limited Smiths, United Kingdom).

All transvaginal ultrasound measurements, oocyte retrievals and embryo transfers were performed by two of the authors who were comparable in success rates.

In each case, luteal phase was supported with progestagen tablets (Duphaston®, Solvay, Holland). The clinical pregnancy with the number of gestational sacs and fetal viability was confirmed by ultrasound at *fifth week* of gestation.

Body Mass Index

BMI values for individual women were calculated by the ratio of body weight (kg) as divided by the height² (m²) (8). Total body weight for the group of subjects ranged between 47 and 110 kg (median: 63 kg). Height ranged between 150 and 179 cm (median: 165 cm).

Statistical Analysis

Data on women's age, height, weight, gynaecological history, basal FSH and LH concentrations on days 1–3 of the cycle, as well as serum E₂, TSH and PRL concentrations, the stimulation protocol used, the number of oocytes aspirated/fertilized, the number

of embryos transferred, and the pregnancy rates per embryo transfer achieved, were recorded.

Statistics were calculated by using the SPSS software (SPSS Inc., Chicago, IL 60606) for Windows 10.0.1 (1999). Multiple logistic regression analysis was used to describe influences of independent factors on dichotomous variables. A backward selection method by means of Wald statistics eliminated non-significant covariates. The odds ratio and the 95% confidence interval was calculated for specification of the progression of pregnancy odds depending on significant influencing factors utilizing the proportional hazard method. The logistic probability of the occurrence of pregnancy was calculated for dominating influencing factors (BMI and FSH) and listed in a table, which should give a guide for clinical practice. For the calculation of this probability a formula is also given derived from the results of the multiple logistic regression analysis. *For significant covariates the median, percentile 25 (1st quartile) and percentile 75 (3rd quartile) were calculated. The regression models were controlled by the goodness-of-fit test of Hosmer and Lemeshow. The independence of predictors was examined with Spearman's correlation analysis. P-values below 0.05 were accepted as significant.*

RESULTS

A total of 171 women (mean age: 34 years) were included in this study. Fifty-seven patients became pregnant. The overall pregnancy rate was 33.3%.

The median of BMI in the sample was 20.5, with a 25-percentile of 22.7 and a 75-percentile of 25.7. FSH values resulted in a median of 4.9 with a 25-percentile of 6.5 and a 75-percentile of 8.1.

The logistic regression analysis was utilized for investigations of influences of the variables age, BMI, LH, FSH, E2, TSH, PRL, endometrium thickness, stimulation protocol used, number of oocytes aspirated/fertilized, and number of embryos transferred on the occurrence of gestation. *The univariate analyses revealed significantly decreasing odds of pregnancy for increasing BMI (kg/m²) and FSH (mIU/mL) (Table I: $p = 0.012$ and $p = 0.039$, respectively). After adjustment of the univariate results by multiple logistic regression models and after examining potential confounding effects between the predictors (Table I), the significance of BMI and FSH was confirmed ($p = 0.014$ and $p = 0.048$, respectively). By raising BMI and FSH by one unit, the odds for pregnancy were decreased by the respective factors 0.84 (95%*

Table I. Univariate Logistic Regression Analyses Suggested BMI and FSH as Significant Predicting Factors for Pregnancy

Variable	Odds ratio (95% CI)	p-value
BMI	0.843 (0.739 to 0.963)	0.012
LH	0.869 (0.690 to 1.096)	n.s.
FSH	0.775 (0.608 to 0.988)	0.039
E2	1.008 (0.996 to 1.020)	n.s.
Prolactin	0.983 (0.917 to 1.055)	n.s.
TSH	1.157 (0.877 to 1.526)	n.s.
Endometrium thickness	0.988 (0.807 to 1.210)	n.s.
Protocol	0.529 (0.191 to 1.462)	n.s.

confidence interval 0.73–0.97) and 0.77 (95% confidence interval 0.59–1.00). Conversely, each reduction of BMI and FSH by one unit increased the chance of pregnancy by the respective average factors of 1.19 and 1.30. *There were no significant interaction effects between BMI and FSH. For getting information on potential lack of validity of the regression model we repeated the analyses on randomly selected subsamples. The above results were confirmed by significance or a trend to significance (data not shown). BMI and FSH were independent predictors (Spearman correlation $r = 0.043$, $p = 0.591$). The Hosmer–Lemeshow test did not significantly refute the goodness of fit of the model ($p = 0.113$).*

There are two reasons for the elimination of the other variables from the logistic regression model. In the first place, the variable did not have any influence on the occurrence of pregnancy. Secondly, an existing influence depended on other significant variables and did not provide an additional information. LH is such a variable. There is a connection with FSH and BMI. Spearman's correlation analysis revealed coefficients of 0.343 ($p < 0.001$) and 0.212 ($p = 0.007$) in respect to FSH and BMI. Regression models without FSH supplied a significant decrease for the odds of gestation for high LH values. *Due to the strong association between LH and FSH similar effects of LH on the odds of gestation could be expected (data not shown).*

The probability for pregnancy depending on BMI and FSH values can be calculated by the formula

$$P(\text{pregnancy}) = \frac{1}{1 + 194.76 \times 0.84078^{-\text{BMI}} \times 0.76854^{-\text{FSH}}}$$

if the unit of FSH is mIU/mL. The coefficients of this formula were derived from the results of the logistic regression analysis. The results are listed in Table II.

Further investigations of potential influences of BMI on endometrium thickness, dosage/duration

Table II. The Probability (%) of Pregnancy Depending on the Main Effective Variables BMI and FSH with 95% Confidence Intervals (CI). The Results are Based on a Sample of 171 Subjects with a Number of 57 Pregnant Women

Pregnancy					
BMI (kg/m ²)	FSH (mIU/mL)	Predicted probability (%) with 95% CI	BMI (kg/m ²)	FSH (mIU/mL)	Predicted probability (%) with 95% CI
18	1	86.9% (59.9%–96.7%)	30	1	45.5% (16.6%–77.8%)
18	2	83.6% (62.1%–94.1%)	30	2	39.1% (17.3%–66.3%)
18	3	79.7% (62.7%–90.2%)	30	3	33.0% (17.0%–54.2%)
18	4	75.1% (61.7%–85.0%)	30	4	27.5% (15.9%–43.3%)
18	5	69.9% (58.9%–79.0%)	30	5	22.6% (13.9%–34.5%)
18	6	64.1% (54.5%–72.7%)	30	6	18.3% (11.4%–28.1%)
18	7	57.9% (48.2%–67.0%)	30	7	14.7% (8.7%–23.7%)
18	8	51.3% (40.3%–62.3%)	30	8	11.7% (6.2%–20.9%)
18	9	44.8% (31.3%–59.1%)	30	9	9.2% (4.1%–19.4%)
18	10	38.4% (22.3%–57.5%)	30	10	7.3% (2.5%–19.0%)
20	1	82.5% (56.4%–94.5%)	32	1	37.1% (9.8%–76.3%)
20	2	78.3% (58.5%–90.3%)	32	2	31.2% (10.2%–64.5%)
20	3	73.6% (58.9%–84.4%)	32	3	25.9% (10.0%–52.4%)
20	4	68.1% (57.7%–77.0%)	32	4	21.1% (9.1%–41.7%)
20	5	62.2% (54.7%–69.1%)	32	5	17.1% (7.9%–33.2%)
20	6	55.8% (50.0%–61.5%)	32	6	13.7% (6.3%–27.1%)
20	7	49.3% (43.5%–55.0%)	32	7	10.9% (4.8%–22.9%)
20	8	42.8% (35.7%–50.1%)	32	8	8.6% (3.3%–20.3%)
20	9	36.5% (27.2%–46.9%)	32	9	6.7% (2.2%–18.9%)
20	10	30.6% (18.9%–45.5%)	32	10	5.2% (1.3%–18.7%)
22	1	76.9% (50.9%–91.5%)	34	1	29.5% (5.2%–76.1%)
22	2	71.9% (52.9%–85.4%)	34	2	24.3% (5.4%–64.4%)
22	3	66.3% (53.2%–77.3%)	34	3	19.8% (5.2%–52.5%)
22	4	60.2% (51.7%–68.1%)	34	4	15.9% (4.7%–41.9%)
22	5	53.8% (48.5%–59.0%)	34	5	12.7% (4.0%–33.6%)
22	6	47.2% (43.6%–50.8%)	34	6	10.1% (3.2%–27.6%)
22	7	40.7% (37.2%–44.4%)	34	7	7.9% (2.4%–23.5%)
22	8	34.6% (29.7%–39.7%)	34	8	6.2% (1.6%–20.9%)
22	9	28.9% (22.0%–36.9%)	34	9	4.8% (1.0%–19.7%)
22	10	23.8% (14.9%–35.7%)	34	10	3.8% (0.6%–19.5%)
24	1	70.2% (43.5%–87.8%)	36	1	22.8% (2.5%–77.3%)
24	2	64.4% (45.3%–79.9%)	36	2	18.5% (2.6%–66.1%)
24	3	58.2% (45.4%–70.0%)	36	3	14.9% (2.5%–54.5%)
24	4	51.7% (43.8%–59.6%)	36	4	11.8% (2.2%–44.1%)
24	5	45.1% (40.5%–49.9%)	36	5	9.4% (1.9%–35.8%)
24	6	38.7% (35.6%–41.9%)	36	6	7.4% (1.5%–29.6%)
24	7	32.7% (29.6%–35.9%)	36	7	5.7% (1.1%–25.5%)
24	8	27.2% (23.0%–31.8%)	36	8	4.5% (0.7%–22.9%)
24	9	22.3% (16.5%–29.4%)	36	9	3.5% (0.5%–21.7%)
24	10	18.1% (10.9%–28.5%)	36	10	2.7% (0.3%–21.7%)
26	1	62.5% (34.6%–84.0%)	38	1	17.3% (1.1%–79.7%)
26	2	56.2% (36.1%–74.4%)	38	2	13.8% (1.1%–69.4%)
26	3	49.6% (36.0%–63.3%)	38	3	11.0% (1.1%–58.4%)
26	4	43.1% (34.4%–52.3%)	38	4	8.7% (1.0%–48.2%)
26	5	36.8% (31.2%–42.7%)	38	5	6.8% (0.8%–39.8%)
26	6	30.9% (26.9%–35.3%)	38	6	5.3% (0.6%–33.5%)
26	7	25.6% (21.7%–29.9%)	38	7	4.1% (0.5%–29.2%)
26	8	20.9% (16.4%–26.3%)	38	8	3.2% (0.3%–26.5%)
26	9	16.9% (11.4%–24.3%)	38	9	2.5% (0.2%–25.3%)
26	10	13.5% (7.3%–23.6%)	38	10	1.9% (0.1%–25.4%)
28	1	54.1% (25.2%–80.5%)	40	1	12.9% (0.4%–83.0%)
28	2	47.6% (26.3%–69.7%)	40	2	10.2% (0.5%–74.0%)
28	3	41.1% (26.1%–57.9%)	40	3	8.0% (0.4%–63.9%)
28	4	34.9% (24.6%–46.8%)	40	4	6.3% (0.4%–54.2%)
28	5	29.2% (21.9%–37.6%)	40	5	4.9% (0.3%–45.9%)
28	6	24.0% (18.4%–30.7%)	40	6	3.8% (0.2%–39.4%)
28	7	19.6% (14.5%–25.9%)	40	7	3.0% (0.2%–34.9%)
28	8	15.8% (10.6%–22.8%)	40	8	2.3% (0.1%–32.1%)
28	9	12.6% (7.2%–21.1%)	40	9	1.8% (0.1%–30.9%)
28	10	10.0% (4.5%–20.6%)	40	10	1.4% (0.0%–31.1%)

of medication used, number of oocytes retrieved/fertilized and occurrence of abortus did not show any significant results.

DISCUSSION

Body mass and FSH are known to be of some importance to the maintenance of regular reproductive cycles. This retrospective study focused on the role of female body mass and the influence of the hormonal situation on the response to ovarian stimulation protocol and occurrence of pregnancy. Our data show that for the purpose of raising the odds of pregnancy BMI should be reduced. A low FSH value may cause the same effect. In practice the overall endocrine situation and the interaction of the hormones must be considered.

On the other hand, we found that overweight patients with higher FSH measurements entering IVF treatment do not appear to be at a higher risk for cycle cancellation or a reduction in the number of follicles, oocytes or embryos than their normal-weight counterparts.

The association between obesity, hormonal dysfunction and infertility is well documented, but studies that evaluating the effect of body weight and day 3 FSH levels on IVF outcome are few in number and led to conflicting conclusions.

While women's *increased* body fat is an essential requirement for reproductive efficiency and pregnancy, an extreme excess appears to lead to infertility, an increased risk of miscarriage, and difficulty in achieving good responses to assisted reproductive procedures (8). The largest such investigation was the Nurses Health Study, which was reported in 1994 (20). The results of this study showed that the risk of anovulatory infertility in married infertile nurses increased from a relative risk of 1.3 (95% confidence interval 1.2–1.6) in the group with BMI <24 kg/m² to a rate of 2.7 (95% confidence interval 2.0–3.7) in women with BMI >32 kg/m². These data suggest that even moderately overweight women may have difficulty in conceiving in relation to women of average weight.

In agreement with our findings, the retrospective study of Wang *et al.*, using 3,586 women undergoing IVF, has shown a linear decrease in success rates with increasing BMI (21).

Loveland *et al.* reported that excess weight defined as BMI >25 kg/m² has a negative impact on IVF outcome (22).

Halme *et al.* have found that subjects with a BMI ≥30 kg/m² have a pregnancy rate after treatment that

is only 37% of women within the normal or overweight range (17).

An organized programme of lifestyle modification, including dietary changes and increased exercise, is associated with a marked improvement in pregnancy and ovulation rates and a decrease in the need for high technology treatment options (14). The average weight loss for women was 6.3 kg, which meant that none returned to their ideal weight and that in most cases their BMI was still in the obese range. On the other hand, even a small weight reduction was adequate for achieving improvement in reproductive function.

A basal day 3 FSH measurement is a common screening tool to assess the prognosis of achieving a pregnancy with assisted reproduction (23).

The results of different studies show that the use of FSH is best employed to provide prognostic information for women undergoing IVF treatment. Van der Stege *et al.* describe this test as useful in predicting ovarian stimulation response (24).

IVF outcome is also strongly correlated with both day 3 FSH value, maternal age and antral follicle assessment (25).

Nevertheless, obesity and hormonal function may be independent risk factors for failure in assisted reproduction, and factors other than BMI and FSH have more important influences on COH.

CONCLUSIONS

Various studies have identified adverse effects of excessive body mass and elevated FSH levels on ovulation induction and pregnancy outcome, especially in connection with assisted reproduction. The availability of simple reliable screening tests of predicting IVF outcome would assist clinicians in counseling patients and selecting optimal treatment.

We propose to use the basal FSH level as diagnostic test to inform patients about their chances in assisted reproduction treatment and would suggest that infertile women with an abnormal body mass should be encouraged and helped to lose weight before attempting IVF cycles to improve the outcome of their infertility treatment and to prepare for the stresses of pregnancy.

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